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COMMUNICATION

Cooperative induction in double H-bonding donor/acceptor compounds: Chains vs. ribbons[†]

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Two different types of monodimensional crystalline aggregates formed by squaramides, chains and ribbons, have been studied both in the solid state and *ab initio* with four model compounds. Although ribbons are *a priori* possible, only covalently forced *syn* conformations have been observed. Cooperative induction is postulated to explain the preference for chains instead of ribbons in squaramide crystals.

Crystal engineering, the rational design of new solid supramolecular structures, has become a key topic in the last few years due to the impact that new crystalline materials are having in different areas such as supramolecular chemistry, non-linear optical materials, coordination polymers and pharmaceutical sciences.¹ Different approaches have been historically used to understand and predict the core entity that defines the structure of a particular molecular crystal; Gavezzotti proposed a model based on space group information which reduces the structure to small molecular clusters and calculates lattice energies.² while the pioneering model by Etter is based completely on strong hydrogen bonding as the driving force in the formation of a molecular crystal.³ Finally, the model based on supramolecular synthons, which is a probabilistic model that takes into account only the degree of occurrence of a particular pattern of interaction, has gained much attention.⁴ More recently, Hunter proposed a method based on molecular electrostatic potentials to quantify intermolecular interactions through the estimation of relative H-bond donor/acceptor parameters of the most typical functional groups,⁵ and this approach has been used in virtual cocrystal screenings.⁶

Although isodesmic supramolecular polymerization is frequently observed in one-dimensional supramolecular polymers, cooperativity plays a major role when self-complementary molecules assemble into one-dimensional structures by non covalent interactions due to polarization (induction) of interacting groups.⁷ This phenomenon has been previously HF, DFT and MP2 studied by Danenberg *et al.* with urea and formamide.⁸ This contribution aims to explore cooperativity as the driving force in disquaramides, which produces chains in spite of the fact that the ribbon synthon is stronger.

Secondary squaramides are a family of compounds that exhibit interesting and useful properties as supramolecular synthons. The presence of two donors and two acceptor H-bonding groups in a rigid squaric ring have attracted in the past the attention of researchers in different areas such as medicinal chemistry, enantioselective catalysis and supramolecular chemistry.⁹ In addition, these compounds can exist in different conformations due to the partially restricted rotation of the C-N bond offering different supramolecular synthons with suitable complementary donor/acceptor groups. Recently, we have shown that the anti/anti conformer of disecondary squaramides forms a strong selfassociating head-to-tail motif in the solid state.¹⁰ In this paper we report the crystal structures of four new squaramide compounds showing ribbons and chains in the solid state and rationalize these findings in terms of hydrogen bonding cooperativity.

Disecondary squaramides can form *a priori* two different polymeric structures in crystalline solids since two conformations of the squaramide bond are possible (Fig. 1). Dimethylsquaramide **1** was chosen as the simplest model to study the conformational preference in the solid state since no relevant secondary interactions with other groups are possible.

In order to predict which synthon is the most stable, the approach proposed by Hunter to the analysis of H-bonding interactions was applied. Thus, the molecular electrostatic potential surfaces (MEPS) were obtained on the gas phase using *ab initio* calculations and converted into the corresponding H-bond donor/acceptor parameters α and β . In principle, **1** can exist in three conformations as a result of the rotation of both C–N bonds: *antilanti, anti-syn* and *syn-syn*. Only *antilanti* and *syn-syn*



Fig. 1 Chain and ribbon interaction motifs for compound 1.

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Fig. 2 Hydrogen-bond parameters for the three conformations of 1.

conformations would yield catemeric structures and due to cooperativity effects the existence of crystals with the *antilsym* conformation can be considered unlikely. The H-bond parameters obtained confirm that the *antilanti* conformation would produce the strongest intermolecular interaction (Fig. 2) and, assuming that dispersion and packing effects could be similar for all the possible polymorphs, crystal structures of disquaramides should prefer this synthon.

The interaction of each particular synthon was estimated as the sum over both NH···OC contacts with eqn (1),⁶ where α_i are the H-bond donor parameters, β_i are the H-bond acceptor parameters and the sum represents the sum over both interactions.

$$\Delta E = -\sum_{i}^{2} \alpha_{i} \beta_{i} \tag{1}$$

Density functional theory (DFT) calculations were also performed on H-bonded *anti/anti* and *syn/syn* dimers using Spartan'10 software¹¹ in order to compare with the interaction pairing energy. Geometries were optimized¹² and counterpoise corrections for basis set superposition error (BSSE) were used for the calculation of the interaction energy (Table 1a).¹³ Surprisingly, the relative DFT interaction energies are opposite to those estimated through Hunter's approach (Table 1b). However, this can be explained in terms of a mutual induction effect that makes the second hydrogen bond stronger in the *syn/syn* dimer and weaker in the *anti/anti* dimer (Fig. 3).

This effect was roughly simulated by calculating the H-bond parameters of dimers with only one H-bonding interaction. Geometries of the monomers were minimized independently and then positioned in such a way that only one interaction is possible and with a distance between the NH proton and the carbonylic oxygen fixed at 2.0 Å (Fig. 4). In this simulation, once the first interaction is established, the remaining free NH and CO groups can interact and then a rough estimation of the interaction energy

Table 1 Interaction energies calculated by (a) DFT, (b) using eqn (1)and H-bond parameters for non cooperative dimers and (c) forcooperative dimers

Synthon	Interaction Energy (kJ mol ⁻¹)		
	a	b	с
Antilanti Synlsyn	-56.0 -73.1	-78.7 -51.6	-59.2 - 80.2



Fig. 3 Induction effects favouring and disfavouring the second H-bond.



Fig. 4 MEP surfaces and H-bond parameters after the first interaction of *antilanti* and *synlsyn* conformers.

can be performed using eqn (1). Thus, the interaction energies for the *antilanti* and the *syn/syn* dimers are -59.2 and -80.2 kJ mol⁻¹ respectively (Table 1c). These values are closer to those from DFT calculations and strongly support our hypothesis.

This effect, however, is compensated as monomers are added to the chain. Interaction energies of the terminal monomer are represented in Fig. 5 as a function of the number of molecules in the chain/ribbon aggregate for compound $1.^{14}$ As the aggregate grows, the interaction energy increases in the *anti* conformation while it remains practically constant in the *syn* conformation. Again a cooperative induction effect explains this phenomenon: once the monomer is linked to the *antilanti* aggregate an electronic polarization takes place,¹⁵ which reinforces the interaction with subsequent monomers. However, in the *syn/syn* aggregate there is neither polarization nor increased interaction as monomers are added. This suggests an explanation for why all dialkyl squaramides reported in the Cambridge Structural Database exhibit only the *antilanti* supramolecular synthon.



Fig. 5 Interaction energies of the terminal monomer (*anti/anti:* blue; *synl synr*: red) calculated at the DFT B3LYP 6-31+G^{*} level of theory.



Fig. 6 Crystal structure and Hirshfeld's¹⁷ surface of compound 1.

In order to validate this hypothesis, a polymorphic screening was run with $\mathbf{1}$, yielding in all cases the same polymorph with the predicted *antilanti* catemer structure (Fig. 6).¹⁶

The cyclic disquaramide compound **2** which presents a covalently forced *syn/syn* conformation was designed to study the geometrical features of the catemeric structures with *syn/syn* configuration. Compound **2** can be obtained from diethyl squarate and 1,2-diaminoethane in ethanol. In its crystal structure, the expected NH···OC hydrogen bonding is established between two adjacent molecules forming ribbons with the squaramide rings practically in the same plane (Fig. 7).¹⁸

In order to check whether competitive interactions are able to affect the *a priori* less strong *syn/syn* motif, another macrocyclic compound containing an aromatic group was designed. Compound **3** was obtained in a three-step synthetic route (Fig. 8). Dibromide **3a** was converted into the corresponding diazide **3b** in toluene/DMF, then reduced to the amine **3c** with AlLiH₄, and finally condensed with one equivalent of diethyl squarate in ethanol.

Needles were growth in the reaction crude and the crystal structure of **3** was solved by single crystal XRD.¹⁹ Again, the expected NH···OC hydrogen bonding is established between two adjacent molecules forming ribbons, which are connected through additional CO···H_{aromatic} and π -stacking interactions (Fig. 9). The observed lateral offset stack is in a parallel orientation. The centroid to centroid distance, $d(\pi \cdots \pi)$, is 4.31 Å, interplanar distance 3.55 Å and lateral displacement 2.44 Å.

However, squaramide rings are not coplanar (interplane distance = 1.16 Å) but form a zig-zag arrangement which suggests that the competitive π - π aromatic interactions can disrupt the formation of an optimal planar hydrogen bond. This phenomenon, which has not been observed in any of the polymorphs of dibenzyl squaramide,^{10a} suggests that the cooperativity stabilization in the *antilanti* aggregates overcomes possibly disrupting secondary interactions while the non cooperative *synlsyn* synthon is less resistant to its presence.



Fig. 7 Crystal structure and Hirshfeld's surface of compound 2.



Fig. 8 Synthesis of compound 3.



Fig. 9 Crystal structure and Hirshfeld's surface of 3.

Finally, a fourth model compound containing a new synthon which was observed for the very first time in mono esthersquaramides²⁰ (the dimeric *syn–syn* interaction), was studied. Compound **4** can be readily prepared from diethylsquarate and methylamine in diethyl ether. Only one polymorph was obtained, and its crystal structure reveals ribbons formed by dimers interacting through hydrogen bonding.²¹ The strong self-complementary squaramide/squaramide dimer is linked to the following one in the ribbon through weaker CO···H_{ethyl} interactions (Fig. 10). This suggests that, in absence of competitive donor/ acceptor groups, ribbons are more stable than chains in monosquaramides probably due to the difficulty to align efficiently monomers in a head-to-tail manner without losing the advantage of linear cooperativity.

Cocrystals between disquaramides and strong donor/acceptor complementary functional groups, such as carboxylic acids for the



Fig. 10 Ribbons of dimers in the crystal structure of 4 together with Hirshfeld's surfaces showing the strong dimerization process and the weaker interaction between dimers.

syn conformer or diphenols for the *anti* conformer, although optimal from a geometrical point of view, were not expected to be obtained because the predicted interaction energies (from eqn (1)) of these heterosynthons are lower than that of the squaramidic homosynthon.

To corroborate this prediction, an intensive cocrystal screening with compounds 1 and 3 and a set of carboxylic acids and phenols (including squaric acid and resorcinol), involving reaction crystallization, slow and fast crystallization by diffusion of antisolvents, evaporation and grinding techniques was conducted and did not produce any new cocrystal phase. These findings, demonstrate that the self assembly of squaramide rings is a very strong binding motif, difficult to be perturbed by other competing functional groups in the solid state. Thus, they are very attractive to be exploited as molecular scaffolds in the design of new multicomponent crystalline structures because with a suitable functionalization of the secondary squaramide substituents, complementary coformers could establish strong peripheral interactions with them. In this sense, functionalization of the secondary chains with both donors and acceptor groups together with cocrystallization experiments are now being conducted in our laboratory.

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- 12 The geometries were optimized at the B3LYP $6-31G^*$ level while the interaction energies were calculated at the B3LYP $6-31+G^*$ level.
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- 14 Geometries for the syn/syn aggregates were optimized by DFT (6-31G^{*}) methods while those for the anti/anti aggregates were taken directly from the crystal structure of 1.
- 15 Dipolar moment reflects this effect: it increases as monomers are added to the *antilanti* aggregate but it is constant or zero in odd or even number of units respectively in the *synlsyn* aggregate.
- 16 Crystal data for 1: C₆H₈N₂O₂, Mw = 140.14, monoclinic, *a* = 6.087(4) Å, *b* = 7.307(3) Å, *c* = 16.041(8) Å, *β* = 109.98(3), V = 670.5(6) Å⁻³, *T* = 293(2)K, space group P_{2_1}/c , *Z* = 4, Dc = 1.388 mg m⁻³, μ (Mo-K α) = 0.106 mm⁻¹, 4842 reflections collected, 1619 unique (R_{int} = 0.0355), R_1 = 0.0344, w R_2 = 0.0920, GOF = 1.098{*I* > 2 σ (*I*)}. CCDC-865057 contains the supplementary crystallographic data for 1.
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- 18 Crystal data for **3**: C₈H₁₀N₂O₂, Mw = 166.18, monoclinic, *a* = 4.995(4) Å, *b* = 11.203(7) Å, *c* = 14.389(8) Å, *β* = 94.44(4), V = 802.8(9) Å⁻³, *T* = 105(2)K, space group P_{2_1}/c , *Z* = 4, Dc = 1.375 mg m⁻³, μ (Mo-Kα) = 0.101 mm⁻¹, 6377 reflections collected, 2422 unique ($R_{int} = 0.0555$), $R_1 = 0.0470$, w $R_2 = 0.0882$, GOF = 1.099{ $I > 2\sigma(I)$ }. CCDC-865058 contains the supplementary crystallographic data for **2**.
- 19 Crystal data for **3**: $C_{12}H_{10}N_2O_2$, $\dot{M}w = 214.22$, Orthorhombic, a = 18.938(19) Å, b = 11.841(11) Å, c = 4.309(6) Å, V = 966.3(19) Å³, T = 293(2)K, space group Pnma, Z = 4, Dc = 1.473 mg m⁻³, μ (Mo-K α) = 0.103 mm⁻¹, 8451 reflections collected, 1664 [R(int) = 0.1013], $R_1 = 0.0764$, $wR_2 = 0.1836$, GOF = 1.180 { $I > 2\sigma(I)$ }. CCDC-865059 contains the supplementary crystallographic data for **3**.
- 20 Several crystal structures of mono squaramides are present in the CCDC (ref. ACULEP, ACULIT, ACULIT01, CAQRUH, ETIVIM, IXUVAY, JINRAA, MEGNAO, NEMMEX, and SIXFIP), all showing other different supramolecular synthons.
- 21 Crystal data for **4**: C₇H₉NO₃, Mw = 155.15, Triclinic, *a* = 7.619(14) Å, *b* = 7.888(11) Å, *c* = 8.147(9) Å, α = 65.33(9)°, β = 66.81(8)°, γ = 72.58(10)°, *V* = 403.6(10) Å³, *T* = 293(2)K, space group PĪ, *Z* = 2, Dc=1.277 mg m⁻³, μ (Mo-K α) = 0.101 mm⁻¹, 3151 reflections collected, 1938 [R(int) = 0.0460], *R*₁ = 0.0746, w*R*₂ = 0.1674, GOF = 1.134 {*I* > 2 σ (*I*)}. CCDC-865060 contains the supplementary crystallographic data for **4**.